#42 Appeal Brief
10-5-01
1646



PATENT
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Christine M. Citro
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant: | Robert A. Murgita | Art Unit: | 1646 |
| Serial No.: | 08/879,469 | Examiner: | S. Gucker |
| Filed: | June 20, 1997 | Customer No.: | 21559 |

Title: RECOMBINANT HUMAN ALPHA-FETOPROTEIN AS A CELL PROLIFERATIVE AGENT

BOX APPEAL
Assistant Commissioner For Patents
Washington, DC 20231

SUBMISSION OF SUBSTITUTE APPEAL BRIEF

There is submitted here, in triplicate, a substitute complete appeal brief responding to the Notification of Non-Compliance mailed July 30, 2001. Also enclosed is a Petition for Extension of Time extending the period for reply to September 30, 2001.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Sept. 25, 2001

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PATENT
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BOX APPEAL
Assistant Commissioner For Patents
Washington, DC 20231

APPELLANTS' BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of appellant's notice of appeal that was filed in the above-captioned case on October 16, 2000, of the Examiner's final rejection mailed on April 14, 2000, submitted herewith in triplicate is appellant's brief on appeal.

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## Real Party in Interest

The real party in interest is Martinex R & D, Inc., to whom all interest in the present application has been assigned. The assignment document was recorded in the U.S. Patent and Trademark Office ("the Office") at Reel/Frame 010519/0362.

## Related Appeals and Interferences

There are no currently pending appeals or interferences related to this case.

## Status of Claims

Claims 1-19 and 21-24 are currently pending.

Claims 1-18 and 22-24 have been withdrawn from consideration as being directed to a non-elected invention, leaving claims 19 and 21 in the case.

Claims 19 and 21 were finally rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103(a).

## Status of Amendments

A Reply to the Final Office Action and a Petition to Withdraw the Finality of the Final Office Action were filed on October 16, 2000. No response has been received from the Office and accordingly it is believed that this paper has not been entered.

## Summary of the Invention

As stated on page 2, lines 28-32, and page 3, lines 1-2, of the specification, the invention provides a method of promoting bone marrow cell proliferation in a mammal by administering to the mammal unglycosylated, recombinant human alpha-fetoprotein (rhAFP) produced in a prokaryotic cell (*e.g.*, *E. coli*).

## Issues

This appeal presents two issues:

1. Whether the Examiner erred in rejecting claims 19 and 21 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

2. Whether the Examiner erred in rejecting claims 19 and 21 under 35 U.S.C. § 103(a) for obviousness over Hoskin et al. (Cellular Immunology 96:163-174, 1985; hereafter "Hoskin").

## Grouping of Claims

With respect to both issues, the claims stand or fall together.

## Argument

Issue 1: Rejection of Claims 19 and 21 under 35 U.S.C. § 112, first paragraph

The Examiner asserts that the dosage range recited in the specification is too large and questions, without evidence, whether rhAFP would be efficacious at the upper end of the dosage range, based on the Examiner's speculation that there might be suppressive effects on cells of the immune system at such doses. The Examiner also speculates, again without evidence, that rhAFP, when administered to a mammal, might encounter not only immature bone marrow cells, but also mature T-cells in the bloodstream. Further, the Examiner incorrectly equates the present case with *In re Colianni* (561 F.2d 220, 195 USPQ 150 (CCPA 1977)), solely based on the fact that the present specification, although containing enabling prophetic examples, does not describe a working example of the administration of rhAFP to a mammal.

### Dosage

The Examiner's concern regarding the dosage of rhAFP did not properly form the basis for a lack of enablement rejection, for several reasons.

In the first place, appropriate dosages of rhAFP in any given case are readily determined by standard techniques, and the Examiner has presented no evidence that this is not the case. Of course, optimal dosage will vary from patient to patient, depending on the particular circumstances of their disease. An optimal dose of a drug for

a particular disease is often quite high, even when such a dose has adverse effects. For example, cyclosporine is a commonly used systemic immunosuppressant that is known to cause hypertension, nephrotoxicity, and hepatotoxicity at high doses, and may render a patient susceptible to infection and neoplasia (Physician's Desk Reference ("PDR"), 52nd Edition, Medical Economics Company, Inc., Montvale, New Jersey, 1998, pp. 1882-1889; Exhibit A). The dosage that cause these toxic side effects are recommended doses, administered with the physician's knowledge that these side effects will most probably occur. Further, the PDR provides guidance on how to administer Neoral®, which is an oral formulation of cyclosporine, and how to monitor the side effects of Neoral® administration:

> The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. . . intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy. Emphasis added.

Thus, the PDR clearly advises against predetermined doses and instead recommends optimizing dosages on an individual basis. It necessarily follows that such optimization is standard and routine, and cannot constitute undue experimentation.

Secondly, appellant emphasizes that rhAFP has no suppressive effects on bone marrow cells, which would be expected to be hypersensitive to immunosuppressive compounds. Indeed, as is discussed at pages 18-19 of the specification, bone marrow cells exhibit a strong proliferative response in the presence of recombinant rhAFP.

Furthermore, rhAFP suppresses the responses only of a small subset of fully-differentiated mature T-cells. This subset constitutes autoreactive and cytotoxic T-lymphocytes, and not the whole population of T-cells. Administration of rhAFP, therefore, does not significantly affect the function of the majority of cells in the immune system. As the upregulation of autoreactive and cytotoxic T-lymphocytes can have detrimental effects, exacerbating a variety of autoimmune diseases, suppression of these cells cannot be construed as a harmful effect.

As another consideration regarding the effects of rhAFP at high doses, appellant points out that AFP is a natural substance which is found in large amounts in the human fetus, up to 3000 μg/ml, and up to 500 ng/ml in the bloodstream of pregnant women (Gitlin, D., 1975, Normal biology of α-fetoprotein. *In* Carcinofetal Proteins: Biology and Chemistry, Hirai, H. and E. Alpert (eds.) pp 7-16, Ann. N. Y. Acad. Sci.; Exhibit B). The Examiner's concern regarding the suppressive effects of recombinant rhAFP is baseless.

Furthermore, the Examiner applies a standard of perfection with respect to enablement that finds no basis in the statute or the case law. The Examiner requires that every embodiment falling within the claims and the recited dosage range perform successfully and without side effects, with failures in thought experiments in extreme cases negating enablement. If this were the standard, generic claims would never be allowable, in any instance in which an Examiner can imagine a single sub-optimal

embodiment. This is not the standard the law imposes. For example, in *Application of Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 218 (C.C.P.A. 1976), the Court, in holding that a claimed invention was enabled even though the claims admittedly included inoperative embodiments, stated that "the evidence as a whole, including the inoperative as well as operative examples, negates the PTO position that persons of ordinary skill in this art, given its unpredictability, must engage in undue experimentation to determine which complexes work."

In the present case, even the Examiner would have to agree that there are dosages within the specified range that are not problematical, and as discussed above, the law does not require that all doses in the specified range be optimal.

As stated above, the Examiner also questions whether rhAFP when administered to a mammal will interact not only with immature bone marrow cells, but also with the fully-differentiated mature T-cells in the bloodstream. This concern is based on an abstract co-authored by the inventor of the present invention, Robert A. Murgita, which indicates that fully-differentiated mature T-cells are sensitive to the suppressive effects of rhAFP (Murgita *et al.*, Clin. Exp. Immunol. 33:347-356, 1978; abstract). The Examiner extrapolates from this observation that the skilled artisan would be unable to establish modes, quantities, and length of rhAFP treatment without incurring deleterious effects.

The Examiner has misinterpreted the abstract co-authored by the inventor,

regarding the suppressive effects of rhAFP on cells of the immune system. As is stated above, rhAFP suppresses the responses only of a subset of fully-differentiated mature T-cells, comprising autoreactive and cytotoxic T-lymphocytes, and not the whole population of mature T-cells. Suppression of these autoreactive and cytotoxic T-cells does not cause deleterious effects; thus the issue of predicting the mode, length, and amount of rhAFP to administer so as to avoid these deleterious effects does not arise. Also, as stated above, administration of drugs known to have deleterious effects, for example, cyclosporine, is common. As is the case with many strong medicines like cyclosporine, unpleasant side effects can be expected at high doses, and are accepted as part of the cost-benefit analysis in which the physician engages on behalf of a patient.

The first paragraph of §112 "requires nothing more than objective enablement." *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The Examiner's speculative basis for rejecting the claims is a far cry from the evidentiary- or scientifically-based reasoning on which objective truth or accuracy of

the specification can properly be questioned.

Finally, with respect to the "working example" issue, contrary to the Examiner's position, the instant situation is clearly distinguishable from *In re Colianni* (Paper No. 11, page 7). In contrast to the facts of *Colianni*, appellant's specification (pages 19-22) provides specific examples of methods for promoting bone marrow cell proliferation according to the claimed methods. *Colianni*, unlike the present specification, did not include even one "single specific example of embodiment by way of illustration of how the claimed method is practiced." 195 U.S.P.Q. 152. In addition, unlike *Colianni*, appellant's specification provides no just exemplification but ample guidance on dosages useful for promoting bone marrow cell proliferation.

Issue 2: Rejection of Claims 19 and 21 under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of the claims for obviousness over the Hoskin article. The Examiner (at page 4 of the Final Office Action) states:

> The prior art is equivocal: '...the role of sialic acid in the immunological activity of AFP remains contentious. It is equally possible that the immunoregulatory function of AFP is determined by primary structure rather than by posttranslational modification.' (Hoskin et al., 1985, page 164). Based upon these factors, it would appear that glycosylation of AFP is immaterial to its function, and thus

AFP taught in the prior art is functionally equivalent to that of the instant specification,...

This rejection should be reversed. First, the Hoskin reference does not teach or suggest administration of AFP to promote bone marrow proliferation in a mammal, let alone the use of unglycosylated AFP to do so. Further, the Examiner's argument with respect to biological activity is apparently based on an incomplete reading of Hoskin. Hoskin does not even mention any recombinant human AFP, much less indicate that the normally heavily glycosylated AFP molecule would be biologically active in promoting bone marrow proliferation in an unglycosylated state, as is required by claim 19. Indeed, in contrast to the Examiner's statement, the cited Hoskin passage clearly implies that glycosylation is material to the function of AFP. More specifically, the sentence previous to the one quoted by the Examiner states that "...deglycosylated murine AFP molecules are reported to lack lymphosuppressive activity." (emphasis added). A fair reading of this passage is that glycosylation is most likely very important for the biological functions of AFP. Thus, it is clear that prior to the instant invention, the function of glycosylation in AFP was at best uncertain. Appellant's experiments, as described on pages 16-19 of the specification, were therefore required to demonstrate that unglycosylated AFP retains biological function in the claimed methods. Because the authors of Hoskin cannot have taught what they did not know, their article cannot render the claimed invention obvious.

## Conclusion

Appellants respectfully request that the rejection of claims 19 and 21 be reversed. Also enclosed is a petition to extend the period for replying for one month, to and including September 30, 2001. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Sept. 25, 2001

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## Appendix of Claims on Appeal

19. A method of promoting bone marrow cell proliferation in a mammal, said method comprising administering to said mammal an effective amount of recombinant human alpha-fetoprotein, wherein said recombinant human alpha-fetoprotein is produced in a prokaryotic cell and is unglycosylated.

21. The method of claim 19, wherein said prokaryotic cell is E. coli.